METHOD FOR TREATMENT OF CANCER WITH COMBINATION OF COLD ATMOSPHERIC PLASMA AND A GENE INHIBOTOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of the filing date of U.S. Provisional Patent Application Ser. No. 62/953,754 filed by the present inventors on Dec. 26, 2019.

[0002] The aforementioned provisional patent application is hereby incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0003] None.

BACKGROUND OF THE INVENTION

Field Of The Invention

[0004] The present invention relates to systems and methods for treating cancer with cold atmospheric plasma.

Brief Description Of The Related Art

[0005] Breast cancer is the most common cause of cancer death among women worldwide (F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," CA Cancer J Clin, 68 (2018) 394-424) and it exhibit diverse molecular features that reflect the high heterogeneity which complicates the clinical treatment (N. Howlader, K. A. Cronin, A. W. Kurian, R. Andridge, "Differences in Breast Cancer Survival by Molecular Subtypes in the United States," Cancer Epidemiol Biomarkers Prey, 27 (2018) 619-626). Breast cancer are categorized by the molecular receptor status that are expressed such as the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression. Prognosis for breast cancer patients is generally favorable with ER+/PR+ tumors, intermediate with either ER+/PR− or ER−/PR+ tumors, and usually poor for ER−/PR− tumors. Based on the receptor status selective therapeutic interventions are carried out. For example, in the case of ER+ tumor estrogen-receptor modulators, such as Tamoxifen and letrozole are administered, trastuzumab is (Herceptin), a humanized monoclonal antibody developed to target and inhibit the function of HER2 and a dual anti-HER2 regimen, pertuzumab in combination with trastuzumab and docetaxel are administered to mitigate the risk of mortality to considerable effect, however the incidences of adverse events and resistance to these drugs are not uncommon. Triple negative breast cancer (TNBC) (ER−/PR−, HER2−) do not respond to endocrine therapy or HER2-targeted therapies. Therapies targeting TRAIL (TNF (tumor necrosis factor)-related apoptosis-inducing ligand) and cyclin dependent kinases (CDK) or cell cycle regulators have been used with limited success. In recent years Cold atmospheric plasma (CAP) technology that utilizes ionized gas to selectively induce apoptosis in cancer cells have shown very encouraging results. Preclinical In vivo studies in mouse models for various cancers for CAP treatment have demonstrated to effectively reduce tumor growth rate and induce cancer cell death. CAP treatment induces apoptosis in various breast cancer cells and the potency of the treatment depend on a combination of parameters such as the concentration and the time of the plasma treatment. Susceptibility or resistance to CAP treatment is also determined by the molecular features of the cell types such as the receptor status which are classified into intrinsic subtypes including luminal A (ER+PR+/−HER2−), luminal B (ER+PR+/−HER2+), basal-like (ER−PR−HER2−), and HER2-positive (ER−PR−HER2+). At high concentrations and duration of CAP treatment most of the breast cancer cells often undergo apoptosis due to the release of reactive oxygen and nitrogen species (RONS) and oxidative stress-induced cell toxicity of these species. The mechanism of such oxidative stress-induced cell death process is broadly discussed in various studies. CAP treatment on subtypes of breast cancer cell lines has been demonstrated to reduce breast cancer viability by 92-99% regardless of the status of the receptors on these cells at the most optimal power setting and time of treatment. However, some subset of cells resists the CAP insult and survive, but the molecular mechanism for such survival in these cells has not been systematically investigated.

[0006] Several different systems and methods for performing Cold Atmospheric Plasma (CAP) treatment have been disclosed. For example, U.S. Pat. No. 10,213,614 discloses a two-electrode system for CAP treatement. U.S. Pat. No. 9,999,462 and U.S. Pat. No. 10,023,858 each disclose a converter unit for using a traditional electrosurgical system with a single electrode CAP accessory to perform CAP treatment. WO 2018191265A1 disclosed an integrated electrosurgical generator and gas control module for performing CAP.

SUMMARY OF THE INVENTION

[0007] Breast cancer is the leading cause of cancer death among women. Predominantly, the poor prognosis is due to the triple-negative breast cancer characterized by the absence or low-level expression of estrogen (ER), progesterone (ER), and HER2 receptors. Cold atmospheric plasma (CAP) jet delivered by the Canady Cold Plasma Conversion system that induces cell death in triple-negative breast cancer cell line without thermal damage, however, the mechanism of cell death by CAP treatment is ambiguous. In this study, we aimed to investigate the gene expression profile by screening the expressions of apoptotic and oxidative stress related gene markers in breast cancer cell lines after CAP treatment to determine the molecular mechanism of CAP induced cell death. Six different types of breast cancer cell lines including MCF-7 and T-47D (luminal A: ER+PR+/−HER2−), BT-474 (luminal B: ER+PR+/−HER2+), SK-BR-3 (ER−PR−HER2+), MDA-MB-231 and Hs578T (basal-like: ER−PR−HER2−) were tested with Canady Helios Cold Plasma Scalpel (CHCPS) with 2 power settings (80 p and 120 p, which are approximately 15 W, and 28 W respectively). Gene expression of 48 apoptotic and 35 oxidative gene markers were determined at 4 different time points (3 hrs, 6 hrs 12 hrs and 24 hrs) after treatment with CHCPS, using quantitative real time polymerase chain reaction (qRT-PCR). After CAP treatment, the expression level of BCL2A1 and TNF were significantly increased in triple-negative cell lines, MDA-MB-231 and Hs578T ($p<0.01$). In contrast, the HER2-positive and ER, PR positive cell lines showed little or no expression of BCL2A1 ($p<0.01$). Silencing BCL2A1 mRNA by siRNA increased the potency of the